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Metabolic syndrome, diabetes and atherosclerosis: Influence of gene–environment interaction

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ABSTRACT

Despite remarkable progress in diagnosis and understanding of risk factors, cardiovascular disease (CVD) remains still the leading cause of morbidity and mortality in the world's developed countries. The metabolic syndrome, a cluster of risk factors (visceral obesity, insulin resistance, dyslipidaemia, and hypertension), is increasingly being recognized as a new risk factor for type 2 diabetes and atherosclerotic cardiovascular disease. Nevertheless, there is wide variation in both the occurrence of disease and age of onset, even in individuals who display very similar risk profiles. There is now compelling evidence that a complex interplay between genetic determinants and environmental factors (still largely unknown) is the reason for this large inter-individual variation in disease susceptibility. The purpose of the present review is to describe the current status of our knowledge concerning the gene–environment interactions potentially implicated in the pathogenesis of metabolic syndrome, diabetes and cardiovascular disease. It focuses predominantly on studies of genes (peroxisome proliferator-activated receptor- γ , alcohol dehydrogenase type 1C, apolipoprotein E, glutathione S-transferases T1 and M1) that are known to be modified by dietary and lifestyle habits (fat diet, intake of alcohol and smoking habit). It also describes the limited current understanding of the role of genetic variants of xenobiotic metabolizing enzymes and their interactions with environmental toxicants. Additional studies are needed in order to clarify whether inter-individual differences in detoxification of environmental toxicants may have an essential role in the development of CVD and contribute to the emerging field of “environmental cardiology”. Such knowledge may be particularly relevant for improving cardiovascular risk stratification and conceiving the development of “personalized intervention program”.

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1. Introduction

The American Heart Association reports that cardiovascular disease (CVD) is the leading cause of death in the United States and the cause of more than half of all mortality in the world's developed countries [1]. Major clinical manifestations of cardiovascular disease include myocardial infarction, coronary artery disease, stroke, peripheral artery disease and congestive heart failure. In most cases, these clinical conditions result from atherosclerosis, a progressive disease of the arterial wall, characterized by focal thickening and luminal obstruction [2].

Much of the actual knowledge about CVD was obtained by the very well planned longitudinal, initiated in 1948, Framingham Heart study [3]. The Framingham group has coined the term of “risk factor”, and has contributed enormously to the understanding of the underlying pathologic process leading to CVD. Major well-known

risk factors include hypertension, elevated levels of low-density lipoprotein cholesterol (LDL-C), smoking, and type-2 diabetes.

In addition, the joint occurrence, or ‘clustering’ of multiple metabolic abnormalities has recently led to the introduction of the concept (from Greek meaning “*running together*”) of the metabolic syndrome (MS) [4,5]. This syndrome is associated with an increased risk of type 2 diabetes, accelerated atherosclerosis and cardiovascular events.

Despite advances in pathophysiology and risk factors that predispose to CHD, there are many key aspects that remain unclear. These include variation in susceptibility, and a wide variable age of onset in individuals who display very similar risk profiles.

These differences are mainly attributed to genetic differences or to interactions between genes and environmental factors [6]. However, the polygenic nature of metabolic syndrome and related cardiovascular risk suggests that it is unlikely that a single gene is responsible for the development of the disease. It is more plausible that are many genes each of small effect displaying effect modification in the presence of certain environmental factors (e.g. cholesterol, tobacco and alcohol).

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Table 1
Diagnostic criteria for metabolic syndrome.

Abdominal obesity (waist circumference)	Men ≥ 102 cm (≥ 40 in.) women ≥ 88 cm (≥ 35 in.)
Elevated triglycerides	≥ 150 mg/dl (1.7 mmol/l)
Reduced HDL-C	Men < 40 mg/dl (0.9 mmol/l) women < 50 mg/dl (1.1 mmol/l)
Blood pressure	≥ 130 systolic blood pressure ≥ 85 mmHg diastolic blood pressure
High fasting glucose	110 mg/dL and < 126 mg/dL (without diabetes)

The purpose of the present review is to describe the current knowledge concerning the gene–environment interactions potentially implicated in the pathogenesis of metabolic syndrome, diabetes and cardiovascular disease.

2. Atherogenesis in metabolic syndrome and type 2 diabetes

The clinical characteristics of the MS include insulin resistance, dyslipidaemia, abdominal obesity and hypertension. Any three of the five criteria reported in Table 1 constitute a diagnosis of MS.

The increasing prevalence of MS worldwide seems to be due largely by more obesity that is promoted and exacerbated by sedentary lifestyles. The MS is a powerful and prevalent predictor of diabetes and atherosclerotic cardiovascular events [7]. Adipose tissue plays a vital role in the pathogenesis of the MS, promoting the development of type 2 diabetes mellitus and atherosclerosis. Abdominal fat associated is a major source of the excessive

flux of free fatty acids (FFAs), which are known to affect insulin signal transduction pathway, induce endothelial dysfunction due to increased reactive oxygen species (ROS) generation and oxidative stress [7]. Prolonged release of FFAs is implicated in the development diabetes since it promotes insulin resistance and the associated loss of pancreatic beta-cell function (Fig. 1).

Insulin resistance is also itself a risk factor for CVD. It blunts vascular production of nitric oxide, a factor crucial to the normal vasodilatory response and endothelial function [8].

Moreover, glucose intolerance and hyperglycemia facilitate the accelerated formation of advanced glycation endproducts (AGEs), that are a heterogeneous group of molecules formed from the nonenzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. AGEs interact with receptor for advanced glycation endproducts (RAGE) to activate numerous intracellular signaling pathways implicated in the atherosclerotic pathway [9,10].

Numerous animal and human studies have shown that AGEs and their receptors critically contribute to amplify inflammatory responses through enhanced generation of proinflammatory adhesion molecules, cytokines, and tissue-destructive matrix metalloproteinases [11]. In addition to those endogenously formed, AGEs can also be introduced in the body from exogenous sources. For instance, tobacco smoke is a well-known exogenous source of AGEs [12]. Furthermore, diet is an important source of exogenous AGEs, with the highest content found in heat-treated foods [13].

Moreover, studies in diabetic subjects demonstrated that dietary AGEs increase markers of inflammation (C-reactive protein tumor necrosis factor and endothelial dysfunction vascular cell adhesion

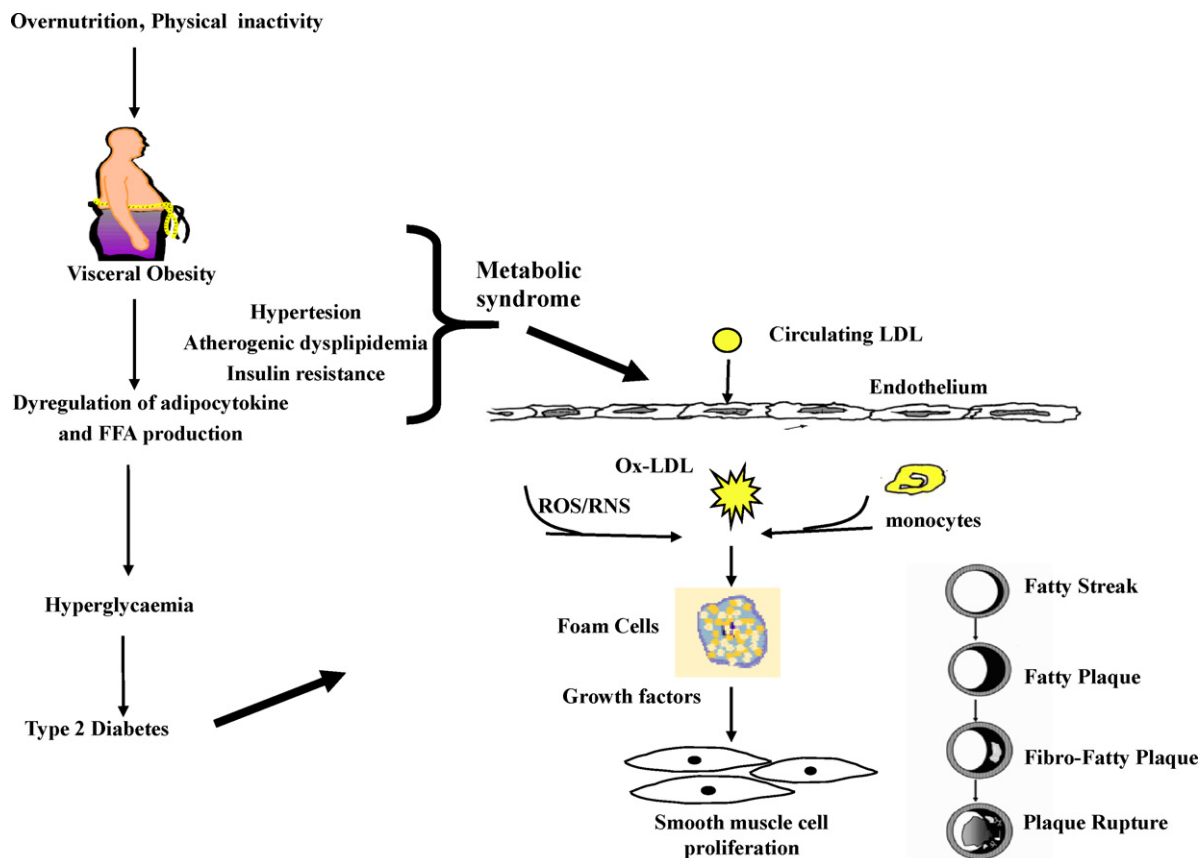


Fig. 1. Progression and outcomes of the metabolic syndrome. The metabolic syndrome arises largely by visceral obesity, and encompasses each stage in the development of type 2 diabetes and atherosclerosis.

molecule 1) whereas a restriction of dietary AGEs led to suppression of all these markers [14].

Furthermore, visceral obesity is strongly associated with high plasma triglycerides and low plasma high-density lipoprotein-cholesterol (HDL-C), and with high plasma concentrations of apolipoprotein B (apoB)-containing lipoproteins. Dyslipidemia contributes to a proinflammatory state and atherosclerosis, that, indeed, is considered a low-grade chronic inflammatory disease [2]. Atherosclerotic lesion begins with “fatty streak” lesions in the artery walls, due to the presence of inflammatory cells and the accumulation of lipid-containing intimal macrophages (foam cells). Early lesions can continue to develop through several stages, ultimately ending with a complex plaque accumulated in the artery wall, which blocks blood flow and can precipitate acute clinical manifestations (Fig. 1).

Acute clinical events, such as myocardial infarction or stroke, are often the result of rupture or ulceration of an “unstable” or “vulnerable” plaque which do not appear severe on angiography. The mechanisms responsible for plaque vulnerability remain, however, poorly defined. Inflammation, thrombosis and apoptosis across all vascular cell type are seen to be key players in atherosclerotic plaque instability and rupture [2,15].

The appearance of atherosclerotic lesions is generally similar in patients with and without diabetes; however, patients with type 2 diabetes show more advanced lesion development, and atherosclerosis tend to be more diffuse and not focal [7].

The pathogenesis of atherosclerosis is closely related to molecular mechanisms, including the modulation of oxidation-sensitive signaling, the expression of cytokines and adhesion molecules, the recruitment of macrophages and T cells, and the consequences of chronic inflammatory conditions in general [2].

Furthermore, there is now accumulating evidence that supports a critical role for DNA damage and telomere dysfunction in the

atherogenic process, probably affecting the vascular function of both endothelial and smooth muscle cells [16].

3. Genetic instability in vascular pathobiology: new evidence for atherogenesis

Every cells are daily attacked by numerous genomic insults, both from intracellular cellular metabolism and exposure to environmental agents (e.g. ionizing radiation, chemicals and toxin pollutants) capable of interacting with the DNA.

Indeed, it is well-known that DNA damage can occur in cells exposed to oxidative stress. Several well-known atherosclerotic risk factors are likely mediators of oxidative DNA damage [16]. For instance, the peroxidation of lipids produces a variety of products (e.g. epoxides, aldehydes, etc.), which are themselves reactive and able to interact with DNA [17].

Metabolic syndrome induces an increase in oxidative stress and may be one of the triggers for increased oxidative DNA damage and telomere shortening of endothelial progenitor cells, promoting endothelial dysfunction [18]. Furthermore, increased oxidative DNA damage in type 2 diabetes is well documented, and it has been suggested that it may be an useful clinical marker in order to predict complications associated with diabetes, such as microangiopathy and macroangiopathy [19–23]. Recently, we have also found that diabetes is one major determinant of chromosomal DNA damage in patients with or without coronary artery disease [24].

This is consistent with a large body of evidence supporting the notion that oxidative stress-induced-genetic instability is a relevant contributor of atherosclerotic plaque development and its complications [25–29].

At vascular level, the loss of heterozygosity and microsatellite instability have been reported in DNA extracted from atherosclerotic plaques, compared to DNA extracted from adjacent normal

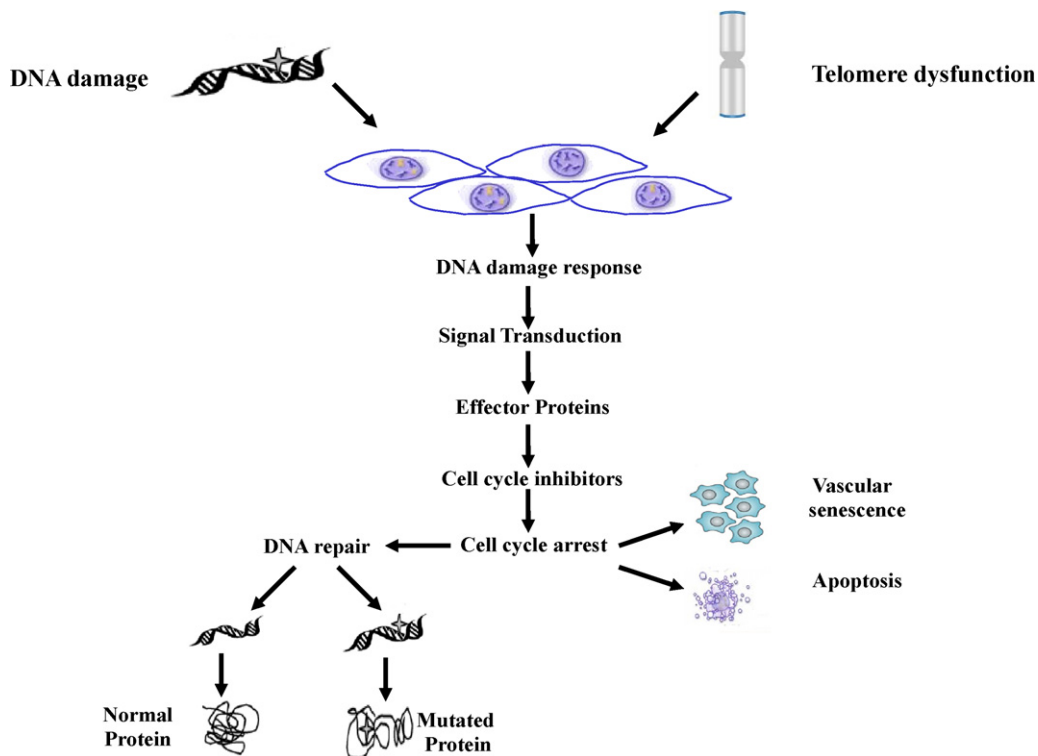


Fig. 2. Simplified representation of the DNA damage response pathway. This pathway involves a highly complex DNA-damage response network, able to sense the damage, then to transduce specific signals into cells, and finally to cause cell cycle arrest for ensuring DNA repair. If DNA damage is non-corrected by the DNA repair mechanisms, it may lead to altered cellular functions. The cell cycle can be also blocked permanently, leading to a senescent state of the vascular cell or apoptosis.

tissue, suggesting that specific molecular alteration of target genes could be an important molecular mechanism associated to the atherogenic process [30–33].

In addition, single or associated clonal chromosomal abnormalities were found in primary cell cultures from human atherosclerotic plaques. More recently, Matturri et al. showed that unstable atherosclerotic plaques presented a variety of chromosomal abnormalities in carotid endarterectomy specimens [34]. Conversely, stable plaques did not present any chromosomal abnormalities, supporting the hypothesis that genetic instability might be of particular importance in the mechanisms of plaque evolution.

DNA adducts have also been detected in SMCs of human abdominal aorta affected by atherosclerosis, and their levels were significantly correlated with known atherogenic risk factors including age, number of currently smoked cigarettes, arterial pressure, blood cholesterol and triglycerides [35]. Moreover, high levels of DNA adducts were found in heart tissue from patients with severe coronary artery disease, especially among smokers [36]. Furthermore, these molecular end-points appear to have a critical role for disease progression and clinical outcome, as demonstrated by recent finding on survival of patients affected by severe atherosclerosis after 14 years of follow-up [37].

A recent study has also shown the presence of high levels of lipid peroxidation-derived etheno DNA adducts in human atherosclerotic lesions, demonstrating the presence of both endogenous (oxidative stress and lipid peroxidation) and exogenous (environmental factors) DNA damage in human atherosclerotic plaque [38].

Furthermore, recent evidence have shown that DNA damage not only do occur in peripheral blood cell levels patients with coronary artery disease and acute myocardial infarction [24,39], but it also affects the long-term clinical outcome [40].

There was also ample evidence to suggest that the telomere dysfunction is another key molecular events in the pathogenesis of cardiovascular and metabolic diseases [41,42]. Telomeres are necessary for the genomic stability and integrity, preventing chromosomal fusion by cellular DNA repair processes.

Dysfunctional telomeres, can lead to genomic instability, and telomere length is an important factor in the pathobiology of human disease [43,44].

Progressive telomere shortening has been demonstrated in peripheral blood cells from patients with metabolic syndrome, diabetes mellitus, coronary heart disease and premature myocardial infarction [11,45–47]. Importantly, accumulating data demonstrate that both telomere shortening and DNA damage are crucial mediators for vascular dysfunction by activating the DNA-damage response pathway [48–51].

This pathway involves a highly complex DNA-damage response network, able to sense the damage, then to transduce specific signals into cells, and finally to elicit appropriate cellular responses, affecting both endothelial and vascular smooth muscle cell functions [15,48–54].

If DNA damage is severe or its accumulation exceeds its elimination by DNA repair mechanisms, cellular vascular senescence or apoptosis will occur and this, in turn, contribute to the atherogenesis process (Fig. 2).

At the present time, genetic instability is, thus, part of the pathogenetic mechanism of metabolic and vascular dysfunction, representing an additional dimension in order to better understanding gene–environment interactions [55].

4. Gene–environment interactions and cardiovascular disease

Despite the progress in the vascular biology, the pathogenesis of CVD remains complex, and has not been fully elucidated.

Specifically, understanding of the genetic basis underlying the pathological sequelae of atherosclerotic development is one of the major challenge in the area of vascular biology [6]. It is generally considered that the genetics of metabolic and cardiovascular diseases involves a large number of genes with common alleles having weak effects on disease risk, but possibly interacting with each other and with environmental factors could act synergistically in the pathogenesis of MS and its complications (Fig. 3) [56]. Several well-documented environmental variables increase the risk of metabolic syndrome and cardiovascular disease, such as dietary fat, smoking and alcohol consumption [57–59].

The interaction of functional gene polymorphisms with environmental factors (gene–environment interactions) may play a substantial role in CHD risk only when an individual with a high-risk genetic profile enters a high-risk environment, will the effect on risk be so great that premature CHD develops (Fig. 3). Indeed, a large number of studies have shown significant gene–environment interactions in the etiology of obesity as well in the pathogenesis of type 2 diabetes and CHD [60–62]. Some selected recent reports of gene–environment interactions, which are associated with significant effects on cardiometabolic risk are described below.

5. Gene–diet interactions and metabolic syndrome

Gene–diet interactions play an important role phenotypes related to obesity and metabolic syndrome [60,61]. In particular, peroxisome proliferator-activated receptor- γ 2 isoform (PPAR- γ 2) is shown to be one of the most promising candidate genes of common obesity, metabolic syndrome and type 2 diabetes, and an excellent example of the relevance of gene–nutrient interactions [60,61,63–67]. PPAR- γ 2 regulates adipocyte differentiation and lipid and glucose metabolism. Several variants in the PPAR- γ 2 gene have been reported, among them the Pro12Ala polymorphism which is associated with increased insulin sensitivity and reduced risk for the development of diabetes [63,64]. Presumably, it may have a protective effect on myocardial infarction [63,64]. The Quebec Family Study suggest that the PPAR- γ 2 Pro12Ala polymorphism can modulate the association between dietary fat intake and components of the metabolic syndrome [65].

In this study it was found a higher body mass index (BMI), visceral adipose tissue area, waist circumference and fasting glucose concentrations in Pro12 homozygotes, but these associations were not observed among carriers of the Ala allele [65]. In addition, carriers of Ala allele did not respond to a higher fat diet, as did carriers of the Pro12 allele [65].

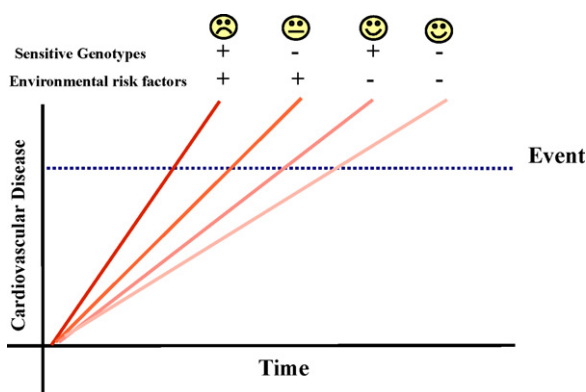


Fig. 3. Schematic representation of gene–environment interaction. Genes and environment risk factors alone do not trigger a cardiovascular event, that only occurs when an individual at high genetic risk enters a high-risk environment.

The findings of a recent randomised controlled trial have also provided a strong evidence supporting the view of a gene-diet weight-related interaction regarding the Pro12Ala polymorphism of PPAR- γ 2 [66]. In this study 522 subjects with impaired glucose tolerance were randomly assigned to an intensive diet and exercise intervention group or a control group. By year 3 of the intervention the odds ratio for the development of type 2 diabetes in subjects with the Ala allele was found to be twofold higher compared with that for the Pro12Pro genotype [66]. However, within the dietary and exercise intervention groups none of the Ala12 homozygotes developed diabetes during the trial [66].

Gene-nutrient interactions can also be modified by other non-nutrient environmental factors, such as physical activity. It has been observed that the relationship of diet and activity with fasting insulin level in Ala carriers is multiplicative, and fasting insulin level is only attenuated when both dietary fatty acid composition and physical activity are simultaneously elevated within the context of type 2 diabetes risk [67]. These findings indicate, therefore, that beneficial changes in diet, increases in physical activity, and weight loss may reverse, to some extent, the diabetogenic impact of the Ala12 allele, possibly due to an improved insulin sensitivity.

6. Moderate alcohol consumption and cardiovascular protection

Another example of the gene-environment relationship on risk of metabolic syndrome and its complications is related to the alcohol consumption. Recently, it has been reported that heavy drinking, in particular among liquor drinkers, is associated with an increased risk of the metabolic syndrome by influencing its components [68].

On the other hand, mild to moderate alcohol consumption, especially of beer and wine, is associated with a lower prevalence of the metabolic syndrome and with a favorable influence on serum lipids, waist circumference, and fasting serum insulin [69]. Specifically, the subjects who consumed 1–19 alcoholic drinks per month had a 35% reduction in risk, and those who had 20 or more drinks each month had a 66% reduction in risk of MS [69]. In addition, recent studies suggest that light to moderate drinking may protect against the development of diabetes [70,71]. This is consistent with observations that low to moderate amounts of alcohol intake increase insulin sensitivity [72,73]. In addition, moderate alcohol consumption also reduce the risk of coronary artery disease and cardiovascular mortality compared with abstinence [74,75].

However, the beneficial effect of moderate alcohol consumption is modified by variation a functional polymorphism in alcohol dehydrogenase type 1C (ADH1C).

At the ADH1C locus, two polymorphisms occur at amino acids 271 and 349 that are in nearly complete linkage disequilibrium [76]. The γ 1 subunit has a 2.5-fold higher V_{\max} for ethanol oxidation than that for γ 2 and has a prevalence of 50–60% among Caucasian populations [76].

Moderate drinkers who are γ 2 γ 2 homozygous for the slow-oxidizing ADH1C allele have a substantially decreased risk of myocardial infarction and coronary artery disease [77–79].

The benefit from moderate alcohol consumption is mainly due to increased HDL concentrations that protect against the development of atherosclerosis [78]. Ethanol itself directly increases HDL in a dose-dependent manner [80]. Thus, this polymorphisms, associated with a slower gastric and hepatic metabolism of ethanol, would lead to increased HDL cholesterol concentrations and reduced cardiovascular risk. In addition, the ability of ethanol to potentially inhibit peroxynitrite-induced DNA strand breakage might have implications for the cardiovascular protection associated with moderate consumption of ethanol [81].

7. Tobacco, genes and cardiometabolic risk

Tobacco smoke exposure is the strongest known environmental risk factor for atherosclerotic vascular disease [82]. In addition, exposure to tobacco smoke, whether by active or passive smoking, is associated with at least a fourfold increase in the risk of the metabolic syndrome among adolescents who are overweight and at risk for overweight [83].

Moreover, cigarette smoking increases the risk for development of microvascular as well as macrovascular complications and mortality in diabetes [84]. The effect of cigarette smoking on diabetic vascular complications involves many metabolic and biological processes, such as endothelial injury, oxidation of low-density lipoprotein and changes in the hemostatic system [85].

Cigarette smoking can initiate/accelerate atherogenesis either directly by causing endothelial dysfunction, vascular smooth muscle cell proliferation in the arterial wall, or indirectly by altering other risk factors such as lipid abnormality, procoagulant status, and oxidative stress [86–88]. Atherogenic effects of cigarette smoking also could be mediated through increase in the formation of DNA alterations by mutagens found in tobacco smoke, which, in turn, may lead to genetic alterations in blood vessels and the heart [26,36–38].

However, susceptibility to adverse health effects to cigarette smoking varies significantly from individual to individual, and only some individuals exposed to cigarette smoke will develop disease whilst others will not [89]. Therefore, the interaction of functional gene polymorphisms with smoking is believed to play a substantial role in individual risk to smoking exposure. During the last years, several studies have examined the impact of gene-smoking interactions on CVD risk [89].

For instance, there is good evidence for a significant interaction between smoking status and apolipoprotein (apoE) genotypes on CHD risk [62]. The common isoforms of apoE, ϵ 2, ϵ 3, and ϵ 4, are important determinants of plasma lipid concentrations, and the ϵ 4 allele has long been recognized as a risk factor for coronary heart disease [90]. In addition, smoking increases the risk of atherosclerotic disease in patients carrying the ϵ 4 allele compared with the non-smoking patient [91–93]. The inter-subject variability in smoking-induced metabolic and vascular diseases can be also partly mediated by genetic variants of genes that may participate in the activation and detoxification processes [89].

For instance, a recent cross sectional case-control analysis of participants in a health screening program demonstrated that the combined presence of glutathione S-transferase genes (GSTT1+/GSTM1+) afforded protection against type 2 diabetes, and the null GSTT1– genotype or the combinations of the null GSTT1– and/or GSTM1– genotypes were independent risk factors for development of type 2 diabetes [94]. Furthermore, the GST null genotypes and the current-smoking status were interactively associated with the incidence of type 2 diabetes [94].

The genetic absence of the GSTT1 enzyme has been also associated with the progression of diabetic retinopathy as well as with an increased cardiovascular morbidity and mortality in patients with type 2 diabetes [95]. Indeed, several studies have investigated the effect between cigarette smoke and GSTM1 and GSTT1 deleted genes on atherosclerotic risk [96–105]. Interestingly, a recent study showed that the adverse effect of oxidative DNA damage on survival of patients with severe atherosclerosis was mainly exerted in subjects bearing either the GSTM1 or the GSTT1 deletion [37].

Overall, these studies show that deleted GSTT1– and GSTT1– polymorphisms contribute to development of atherosclerosis, especially among smokers [96–105].

Interestingly a recent large case-control study investigated the possible interplay between smoking habits, cruciferous veg-

etable consumption, GST genotypes and myocardial infarction [106].

High consumption of cruciferous vegetables, a major dietary source of antioxidant isothiocyanates, might be a possible defense mechanism against oxidative damage, thus lowering CVD risk [107,108]. However, consumption of cruciferous vegetables was associated with a lower risk of myocardial infarction among persons with the functional GSTT-1 gene, but not among those with the GSTT-1 deleted genotype [106]. In addition, the protective effect among those with the GSTT1-1 gene was greater for current smokers than for nonsmokers [106]. These findings strongly suggest that inter-individual variations in enzymes involved in detoxification of xenobiotics and reactive oxygen species may an essential role in the development of CVD and contribute to the emergent field of “environmental cardiology” [109].

8. The emerging discipline of “environmental cardiology”

The idea that the environment significantly influences CVD is not new, however, little is known in regard to how various drugs, chemicals, and pollutants affect CVD [109]. At the present time, a clear role of environmental toxins in affecting heart disease is beginning to emerge [109,110].

In addition to tobacco smoke, certain carcinogenic environmental agents, including arsenic, dioxin and ionizing radiation exposures, have been described to be proven atherogens [26,111].

Recently, epidemiological studies have also shown that chronic accumulation of low concentrations of environmental pollutants within the body is associated with the prevalence of insulin resistance, metabolic syndrome and diabetes [112–115].

Furthermore, it is increasingly being recognized that air pollution exposure is a risk factor for the development of specific cardiac events [116], including life-threatening arrhythmia [117,118] and myocardial infarction [119]. However, the mechanisms of the vascular injury and proatherogenic effects from environmental toxins are not are not fully understood. The many mechanisms of adverse cardiovascular effects are believed to involve inflammation and oxidative stress [109,110,120]. In fact, recent data have shown that both short-term and long-term exposures are associated with increased levels of inflammatory markers [121,122], and that people with MS have a higher degree of inflammatory responses to ambient air pollution [123]. In particular, long-term exposure to particulate air pollution may contributes to systemic oxidative stress, inflammation, progression of atherosclerosis, and risk of ischemic heart disease and death [124]. Short-term exposure may contribute to complications of atherosclerosis, such as plaque vulnerability, thrombosis, and acute ischemic events, especially among patients with underlying coronary artery disease [125].

Furthermore, the results from animal experimental models and in vitro toxicological research have shown that toxicant exposure induces several types of adverse vascular effects, including cytotoxicity, DNA damage and apoptosis [126–128].

Therefore, exposure to environmental toxicants may play a role in the onset and progression of atherosclerosis by inducing somatic mutation, resembling a benign tumor derived from the mutation of vascular cells [26,36–38].

Consequently, individual genetic differences in the ability to metabolize toxicants or repair DNA damage may result in a different susceptibility towards the environmental toxicants and, therefore, increase the risk of developing exposure-related disease [129–131].

However, the link between the individual susceptibility to environmental toxicants and the risk of metabolic and cardiovascular diseases is very poorly documented.

9. Concluding remarks and future perspectives

Despite of remarkable progress, in the management of the “traditional” risk factors, CVD remains a major cause of morbidity and mortality worldwide. The metabolic syndrome is particularly important because its prevalence has increased dramatically in recent years, and it is a risk factors for both CVD and type 2 diabetes.

The dietary modification and increased physical activity are though to be the most effective preventive strategies for the metabolic syndrome in order to prevent the development of diabetes mellitus and cardiovascular disease.

Anyway, it is clear that identifying the molecular mechanisms and risk factors of MS will lead to better understanding of its pathogenesis and complications.

Actually, there is growing evidence to indicate that oxidative damage to DNA may represent an important link between metabolic syndrome, diabetes mellitus, inflammation and atherosclerosis. However, the role of DNA-damage attention remains a poorly understood process in the pathogenesis of CVD. In particular, establishing conclusively whether DNA damage plays a causative role in atherosclerosis development, thrombosis, and plaque rupture still remains to be established. Studies focusing on the DNA repair mechanisms and use of gene-targeted animal models exhibiting tissue-specific alterations in the major DNA repair pathways could be important for determining whether DNA damage plays a causative role or is secondary effect resulting directly from an increased oxidative stress. Clinical research must seek to define whether reduce DNA damage may be a new pharmacological strategy for cardiovascular risk prevention in patients with metabolic syndrome.

Finally, compelling evidence indicate that an interplay of both environmental and common genetic factors can dramatically impact on the development of the metabolic syndrome, type 2 diabetes and CVD. However, additional studies are required in order to better define genotype–phenotype relationships and, further, elucidate key pathways in metabolic and cardiovascular pathophysiology.

For instance, further studies of individual susceptibility to environmental toxicants are needed in order to understand the putative biological mechanisms linking environmental toxicants to atherosclerotic vascular diseases.

Further research will require very large sample size, a better assessment of environmental exposure and robust genetic approaches, such as the use of high-throughput genotyping platforms, in order to improve the understanding in gene–environment interactions and their role in CVD risk.

These advances will be particularly relevant for improving cardiovascular risk stratification and conceiving the development of “personalized intervention program”.

Conflict of interest

None.

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